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# United States Patent [19]

Rosenblum et al.

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[54] **HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS**

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[21] Appl. No.: **617,751**

[22] Filed: **Mar. 18, 1996**

**Related U.S. Application Data**

[63] Continuation-in-part of PCT/US94/10099, Sep. 14, 1994, continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, Sep. 21, 1993, abandoned.

[51] **Int. Cl.**[6] ..... **C07D 205/08**; A61K 31/395

[52] **U.S. Cl.** ..... **514/210**; 540/200

[58] **Field of Search** ..... 540/200; 514/210

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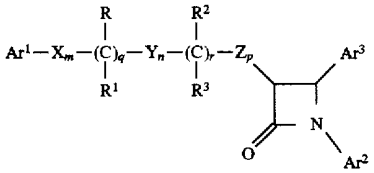
[57] **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

$Ar^1$ and $Ar^2$ are aryl or $R^4$-substituted aryl;

$Ar^3$ is aryl or $R^5$-substituted aryl;

X, Y and Z are $—CH_2—$, —CH(lower alkyl)— or —C(dilower alkyl)—;

R and $R^2$ are $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$ or $—O(CO)NR^6R^7$;

$R^1$ and $R^3$ are H or lower alkyl;

q is 0 or 1; r is 0 or 1; m, n and p are 0–4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1–6; and provided that when p is O and r is 1, the sum of m, q and n is 1–5;

$R^4$ is selected from lower alkyl, $R^5$, $—CF_3$, —CN, $—NO_2$ and halogen $R^5$ is selected from $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$, $—O(CH_2)_{1-5}OR^6$, $—O(CO)NR^6R^7$, $—NR_6R^7$, $—NR^6(CO)R^7$, $—NR^6(CO)OR^9$, $—NR^6(CO)NR^7R^8$, $—NR^6SO_2R^9$, $—COOR^6$, $—CONR^6R^7$, $—COR^6$, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

$R^6$, $R^7$ and $R^8$ are H, lower alkyl, aryl or aryl-substituted Ic

$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl;

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

**9 Claims, No Drawings**

# HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

The present application is the United States national application corresponding to International Application No. PCT/US94/10099, filed Sep. 14, 1994 and designating the United States, which PCT application is in turn a continuation-in-part of U.S. application Ser. No. 08/257593, filed Jun. 9, 1994, U.S. Pat. No. 5,631,365, which is a continuation-in-part of U.S. application Ser. No. 08/102,440, filed Sep. 21, 1993, abandoned.

## BACKGROUND OF THE INVENTION

The present invention relates to hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol bioxynthesis inhibitor for the treatment and prevention of atherosclerosis. The invention also relates to a process for preparing hydroxy-substituteid azetidinones.

Atherosclerotic coronary heart disease (CHD) represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigar smoke and serum cholesterol. A total cholesterol level in excess of 225–250 mg/dl is associated with significant elevation of risk of CHD.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidinones have been reported as being useful lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. No. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in *Indian J. Chem.*, Sect. B. 29B, 12 (1990), p. 1134–7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents. European Patent Publication 264,231 discloses 1-substituted-4-phenyl-3-(2-oxo-alkylidene)-2-azetidinones as blood platelet aggregation inhibitors. European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

WO93/102048, published Feb. 4, 1993, discloses substituted β-lactams useful as hypocholesterolemic agents.

The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteinis. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

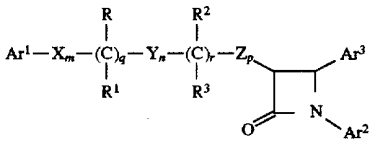


When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL), production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, 80, 5 (1989), p. 1101–1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, Drugs, 36 (Suppl. 3) (1988), p. 63–71).

## SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

$Ar^1$ and $Ar^2$ are independently selected from the group consisting of aryl and $R^4$-substituted aryl;

$Ar^3$ is aryl or $R^5$-substituted aryl;

X, Y and Z are independently selected from the group consisting of —$CH_2$—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and $R^2$ are independently selected from the group consisting of —$OR^6$, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

$R^1$ and $R^3$ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or5;

$R^4$ is 1–5 substituents independently selected from the group consisting of lower alkyl, —$OR^6$, —$O(CO)R_6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —$NR^6R^7$, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —$COR^6$, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH=CH—$COOR^6$, —$CF_3$, —CN, —$NO_2$ and halogen;

$R^5$ is 1–5 substituents independently selected from the group consisting of —$OR^6$, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —$NR^6R^7$, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —$COR^6$, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

$R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl.

$R^4$ is preferably 1–3 independently selected substituents, and $R^5$ is preferably 1–3 independently selected substituents. Preferred are compounds of formula I wherein $Ar^1$ is phenyl or $R^4$-substituted phenyl, especially (4-$R^4$)-

substituted phenyl. $Ar^2$ is preferably phenyl or $R^4$-substituted phenyl, especially (4-$R^4$)-substituted phenyl. $Ar^3$ is preferably $R^5$-substituted phenyl, especially (4-$R^5$)-substituted phenyl. When $Ar^1$ is (4-$R^4$)-substituted phenyl, $R^4$ is preferably a halogen. When $Ar^2$ and $Ar^3$ are $R^4$- and $R^5$-substituted phenyl, respectively, $R^4$ is preferably halogen or —$OR^6$ and $R^5$ is preferably —$OR^6$, wherein $R_6$ is lower alkyl or hydrogen. Especially preferred are compounds wherein each of $Ar^1$ and $Ar^2$ is 4-fluorophenyl and $Ar^3$ is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —$CH_2$—.$R^1$ and $R^3$ are each preferably hydrogen. R and $R^2$ are preferably —$OR^6$ wherein $R^6$ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —$CH_2$ and R is —$OR^6OR_6$, especially when $R^6$ is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —$CH_2$— and $R^2$ is —$OR^6$, especially when $R^6$ is hydrogen.

Another group of preferred compounds is that wherein $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl and $Ar^3$ is $R^5$-substituted phenyl. Also preferred are compounds wherein $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl, $Ar^3$ is $R^5$-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl $Ar^3$ is $R^5$-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

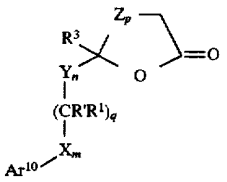
In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

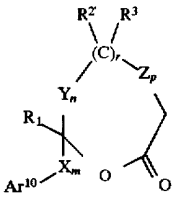
In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula



A

or



B

wherein R' and $R^{2'}$ are R and $R^2$, respectively, or are suitably protected hydroxy groups; $Ar^{10}$ is $Ar^1$, a suitably protected hydroxy substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula

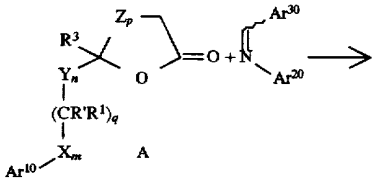
wherein $Ar^{20}$ is $Ar^2$, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and $Ar^{30}$ is $Ar^3$, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

d) optionally removing the protecting groups from R', $R^{2'}$, $Ar^{10}$, $Ar^{20}$ and $Ar^{30}$, when present; and

e) optionally functionalizing hydroxy or amino substituents at R, $R^2$, $Ar^1$, $Ar^2$ and $Ar^3$.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:



A

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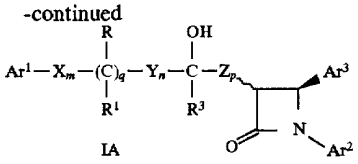
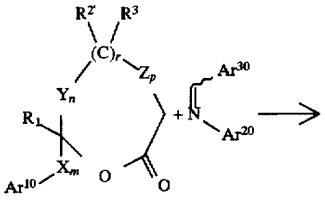


IA

wherein the variables are as defined above; and



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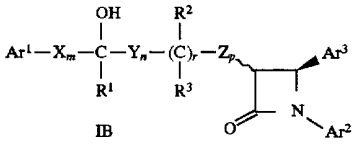


IB

wherein the variables are as defined above.

## DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

"Halogeno" refers to fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein $R^6$, $R^7$ and $R^8$ are said to be independently selected from a group of substituents, means that $R^6$, $R^7$ and $R^8$ are independently selected, but also that where an $R_6$, $R^7$ or $R^8$ variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is —$OR^6$ wherein $R^6$ is hydrogen, $R^4$ can be —$OR^6$ wherein $R^6$ is lower alkyl).

Compounds of the invention have at least one asymmetric carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and I isomers in both pure form and in admixture including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

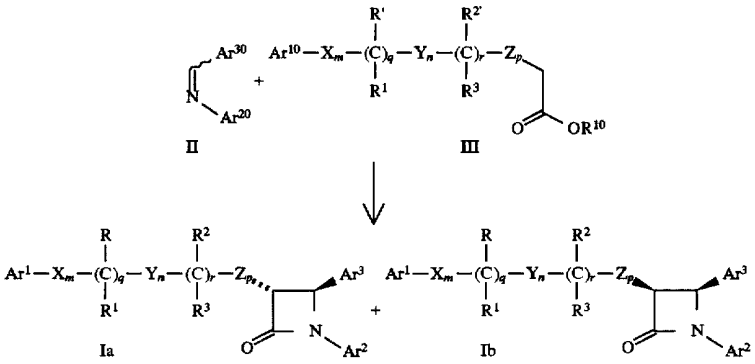
Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and Cl-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'-R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below and in WO93/02048.

Method A:



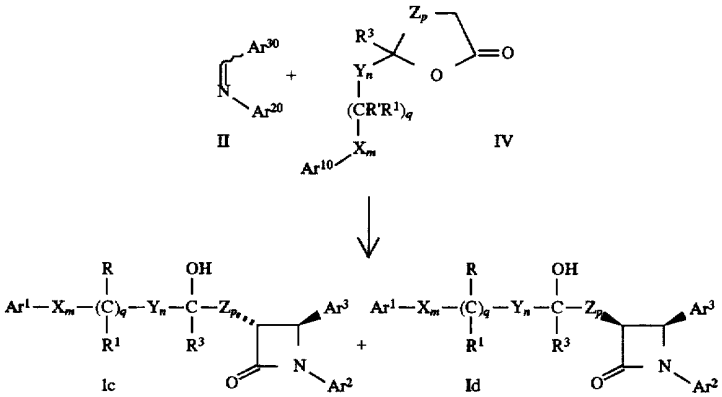
II III

Ia Ib

Compounds of formula Ia and Ib, wherein $Ar^1$, $Ar^2$, Ar3, X, Y, Z, $R^1$, $R^2$, $R^3$, m, n, p, q and r are as defined above, can be prepared by treatment of an ester of formula III, wherein $R^{10}$ is lower alkyl such as ethyl or a chiral moiety such as menthyl or 10-(diisopropylsulfonamido)isobornyl, and the remaining variables are as defined above, with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrrahydrolithium (THF) at −78° C. A solubilizing agent such as hexamethylphosphoric triamide (HMPA) may optionally be added as a cosolvent. An imine of formula 11, wherein $Ar^{20}$ and $Ar^{30}$ are as defined above, is added, the reaction mixture is either warmed to room temperature or maintained at a suitable low temperature such as −78° C. for the appropriate time, followed by quenching with a suitable acid such as 1N HCl. The product is isolated using conventional purification techniques. When a protecting group as defined in Table 1 (below) is present on one or more of the optionally protected groups, an additional step comprising removal of the protecting group by conventional techniques is needed. However, for compounds of formula Ia, Ib, or any compound of formula I wherein a protected hydroxy group $Ar^{10}$, $Ar^{20}$, $Ar^{30}$, R' or $R^{2'}$ is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I. When a chiral ester of formula III is used, the resulting compound of formula Ia or Ib is not racemic.

Imines of formula II ($Ar^{30}$—CH=N—$Ar^{20}$) can be prepared from aldehydes of the formula $Ar^{30}$—CHO and amines of the formula $Ar^{+}$—CHO and by procedures well known in the art. Aldehydes of formula $Ar^{+}$—CHO and amines of formula $Ar^{20}$—$NH_2$ are commercially available or can be prepared via known procedures.

Method A':




Compounds of formula Ic and Id, wherein the variables are as defined above, can be prepared by a process comprising the following steps:

(a) Treat a lactone of formula IV, wherein the variables are as defined above, with a strong base such as an alkyllithium (e.g., n-butyl-lithium), a metal hydride (e.g., sodium hydride), a metal alkoxide (e.g., sodium methoxide), a metal halide (e.g., $TiCl_4$), metal exchange of the lithium enolate with a metal halide (e.g., zinc chloride), metal exchange of the lithium enolate with a metal alkyl (e.g., 9-borabicyclononyl triflate), or, preferably, a metalamide (e.g., LDA), in a suitable anhydrous organic solvent such as dry THF, ether or benzene, in a dry, inert atmosphere, e.g., under nitrogen. The reaction is carried out at about 0° C. to about −85° C., preferably about −78° C., over a period of about 5 to about 60 minutes, preferably about 30 minutes. 1–50% of solubilizing cosolvents may optionally be added, preferably about 10% HMPA.

(b) Add an imine of formula 11, wherein $Ar^{20}$ and $Ar^{30}$ are as defined above, to the product of step (a) over a period of 5 to 60 minutes, preferably 30 minutes, maintaining the reaction mixture at about 0° C. to about −85° C., preferably about −78° C., for 1 to 12 hours, preferably about 3 hours, or warming the reaction mixture over that time period at a rate of about 10° C. per hour to about 70° C. per hour, preferably about 30° C. per hour, to a temperature of about 20° C.

(c) Quench the reaction with a suitable acid such as HCl (1N).

(d) The protecting groups on R', $R^{2'}$, $Ar^{10}$, $Ar^{20}$ and $Ar^{30}$, when present, are removed, if desired, by methods well known in the art, for example silyl protecting groups are removed by treatment with fluoride.

e) Compounds of formula I wherein any of R and $R^2$, when present, are $OR^6$ wherein $R^6$ is hydrogen, can be converted by well known methods to other compounds of formula I wherein R and $R^2$ are functionalized, i.e., are independently selected from the group consisting of $OR^{6a}$, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$, wherein $R^6$, $R^7$ and $R^9$ are as defined above and $R^{6a}$ is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH will afford alkoxy-substituted compounds (i.e., R or $R^2$ is $OR^6$, wherein $R^6$ is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or $R^2$ is —$OC(O)R^6$; treatment of the alcohol with phosgene followed alcohol of the formula $HOR^9$ affords compounds substituted with a —OC(O)$OR^9$ group; and treatment of the alcohol with phosgene followed by an amine of the formula $HNR^6R^7$ affords compounds wherein R or $R^2$ is —$OC(O)NR^6R^7$. Compounds of formula I wherein any $Ar^1$, $Ar^2$ or $Ar^3$ has a hydroxy or amino group can be similarly functionalized to obtain other compounds of formula 1, i.e., wherein $R^4$ and $R^5$ are independently —$OR^{6a}$, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{2-5}OR^6$, —$O(CO)NR^6R^7$, —$NR^6R^7$, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$ or —$NR^6SO_2R^9$.

The product of step c, d or e is isolated using conventional purification techniques such as extraction, crystallization or, preferably, silica gel 60 chromatography. When a chiral lactone is used, the resulting compound of formula Ic or Id is not racemic.

Using the procedure described in steps (a)–(e), lactones of formula IVa can be used to prepare compounds of formula

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